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(54) Title: TREATMENT OF JUVENILE RHEUMATOID ARTHRITIS BY ORAL ADMINISTRATION OF POOLED HUMAN IMMUNOGLOBULIN AND AN ANTACID

(57) Abstract: Pooled human immunoglobulin and optionally an antacid may be administered orally to juvenile rheumatoid arthritis patients to treat the rheumatoid arthritic condition of those patients. Oral administration of pooled human immunoglobulin optionally in conjunction with an antacid results in significant clinical improvement in the level of disease activity in patients with juvenile rheumatoid arthritis.

TREATMENT OF JUVENILE RHEUMATOID ARTHRITIS BY ORAL ADMINISTRATION OF POOLED HUMAN IMMUNOGLOBULIN AND AN ANTACID

FIELD OF THE INVENTION

The present invention relates to the treatment of juvenile rheumatoid arthritis. More particularly, the invention relates to the treatment of juvenile rheumatoid arthritis by oral administration of a pharmaceutical composition comprising pooled human immunoglobulin and optionally in conjunction with an antacid.

BACKGROUND OF THE INVENTION

Juvenile rheumatoid arthritis (JRA) affects one in a thousand children under the age of 17 years and is more common than diabetes, cystic fibrosis and many other chronic conditions. Emery (1998) Adolesc. Med., 9(1):45-48. JRA is most common between 5 and 15 years of age. JRA is characterized by chronic inflammation of the connective tissue membranes that line the spaces between certain bones and moveable joints (synovial membranes).

Clinical manifestations of JRA include high spiking, daily fevers, rash, arthritis, splenomegaly and weight loss. JRA effects males and females with equal frequency.

The immunogenetic associations, clinical course, and functional outcome of juvenile rheumatoid

arthritis are quite different from adult-onset rheumatoid arthritis. Pediatric Rheumatic Diseases In: Primer on the Rheumatic Diseases, 11ed. 1997 (incorporated herein by reference).

Juvenile rheumatoid arthritis is most common in children and includes at least five different forms of disease. One form of juvenile rheumatoid arthritis, Rf-positive polyarticular (i.e., more than 4 joints are involved) juvenile rheumatoid arthritis, bears some resemblance to adult rheumatoid arthritis. However, only about 40% of all juvenile rheumatoid arthritis cases are polyarticular and, of these, only about 5-10% are rheumatoid factor (Rf) positive. Therefore, only 2-4% of juvenile rheumatoid arthritis patients suffer from Rf-positive polyarticular juvenile rheumatoid arthritis. Another form of JRA is Rf-negative polyarticular juvenile rheumatoid arthritis. A third form of JRA is positive antinuclear antibody. A fourth form of JRA is HLA B27 positive and a fifth form is systemic JRA. The onset of JRA may be slow or very rapid. Acute onset JRA is referred to as Still's disease.

Still's disease(also known as systemic onset JRA) is a subset of juvenile rheumatoid arthritis which has systemic features as the major manifestations which include fever, rash, leukocytosis, lymphadenopathy, pleuropericarditis, sore throat and hepatosplenomegaly

are common in addition to arteritis. Classic symptoms of Still's disease include extreme fatique, waves of fevers that rise to 104°F and rapidly return to normal levels, a faint salmon-colored skin rash that does not typically itch. There is also commonly swelling of the lymph glands, enlargement of the spleen and liver, sore throat, joint pain and swelling involving many joints (polyarticular arthritis). Still's disease accounts for 10-20% of all cases of JRA. It affects 25,000 to 50,000 children in the United States and is extremely rare in adults.

Other types of juvenile arthritis include lupus, dermatomyositis, vasculitis and scleroderma and the spondyloarthropathies.

The effective treatment of juvenile rheumatoid arthritis has generally employed a combination of medication, exercise, rest and proper joint protection therapy. The therapy for a particular patient depends on the severity of the disease and the joints that are involved. Aspirin is widely used for pain and to reduce inflammation. In addition to aspirin, non-steroidal anti-inflammatory drugs, corticosteroids, gold salts, anti-malarials and systemic immuno-suppressants are widely used in moderate to advanced cases. The use of steroids and immunosuppressants, however, has significant risks and side effects both in terms of toxicity and

vulnerability to potentially lethal conditions such as infection and malignancy. Thus, there exists a need for a method of treating juvenile rheumatoid arthritis which does not entail the potentially lethal side effects associated with the treatments described above.

One approach to the treatment of autoimmune diseases, of which juvenile rheumatoid arthritis is an example, is tolerization of the patient suffering from the autoimmune disease to the particular autoantigen(s) involved in the disease. In Weiner, et al., Science 259:1321-1324 (1993) (incorporated herein by reference), multiple sclerosis patients were orally administered bovine myelin protein, which contains two multiple sclerosis autoantigens. In Trentham, et al., Science 261:1727-1730 (1993) (incorporated herein by reference), rheumatoid arthritis patients were orally administered collagen, a presumed autoantigen. One drawback to tolerization is the identification of the correct autoantigen to which tolerance is to be induced. Another drawback to tolerization is the potential to induce onset of autoimmune disease. (See Blanas, et al. (1999) Int Rev. Immunol, 18(3):217-228.)

In view of the unsuccessful and disadvantageous modalities currently employed, there is a continued need to develop effective methods and compositions for the treatment of juvenile autoimmune rheumatoid arthritis.

SUMMARY OF THE INVENTION

The present invention is directed to a method and composition for treating juvenile rheumatoid arthritis patients by orally administering an amount of pooled human immunoglobulin which is sufficient to provide a clinically observable improvement in a patient's rheumatoid arthritic condition. The present invention also contemplates oral administration of pooled human immunoglobin in conjunction with an antacid. The present invention is based on the surprising discovery that the oral administration of pooled human immunoglobulin to patients with juvenile rheumatoid arthritis results in a significant clinical improvement in the rheumatoid arthritic condition of the patient. The present invention is also based on the discovery that there are no toxic effects attributed to the orally administered pooled human immunoglobulin to treat juvenile rheumatoid arthritis patients.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

The present invention concerns methods for treating patients with juvenile rheumatoid arthritis. This is accomplished by orally administering pooled human immunoglobulin to the patient, optionally in conjunction

with an antacid. Pooled human immunoglobin is provided in an amount sufficient to provide a clinically observable improvement in the symptoms associated with the patient's rheumatoid arthritic condition. An immunoglobulin, introduced into the acidic environment of the human stomach, may suffer inactivation. To alleviate such inactivation and/or provide increased therapeutic efficacy, the pooled human immunoglobulin employed in the methods and compositions of the present invention is optionally administered in conjunction with an antacid. The present invention also contemplates pharmaceutical compositions comprising pooled human immunoglobulin.

While not wishing to be bound to a particular mechanism, the acid blocker may neutralize the otherwise acidic character of the gut thereby shielding the immunoglobulin from digestion in the stomach. Alternatively, the acid-blocker and immunoglobulin may synergistically provide remediation of arthritis symptoms by suppressing inflammatory mediators or immune-mediated inflammation.

A preferred aspect of the present invention provides pharmaceutical compositions comprising pooled human immunoglobulin and a pharmaceutically acceptable carrier. Another preferred aspect of the present invention provides a pharmaceutical composition comprising pooled human immunolgloblin, an antacid and a

pharmaceutically acceptable carrier. In still another preferred embodiment the composition comprises Sandoglobulin®, cimetidine and a pharmaceutically acceptable carrier.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredients, its use in the therapeutic compositions is contemplated.

As used herein, the term "pooled human immunoglobulin" refers to an immunoglobulin composition containing polyclonal antibodies obtained from the plasma of thousands of human donors. The polyclonal antibodies may include IgG, IgA, IgM, etc. or fragments thereof. A preferred polyclonal antibody is IgG. A preferred immunoglobulin composition contains at least about 90% IgG polyclonal antibodies and trace amounts of other polyclonal antibodies such as, for example, IgA and IgM. Examples of pooled human immunoglobulin compositions useful in accordance with the present invention include, but are not limited to, Sandoglobulin®, Gammagard®,

Gamimune® and Gammar®. In accordance with the present invention any pooled human immunoglobulin can be used.

"Antacid" when used herein denotes an H_2-blocker or acid blocker or other acid neutralizing agent which neutralizes and/or significantly reduces the acidic content of the gut. A preferred antacid useful in accordance with the teachings of the present invention is cimetidine.

A "clinically observable improvement" when used herein refers to a significant subjective remediation and/or objective remediation of symptoms associated with the patient's rheumatoid arthritic condition including, but not limited to, tender joint(s), swollen joint(s) and stiffness assessments. Significant subjective remediation of symptoms denotes a patient's self-assessment or a physician's assessment of stiffness, joint tenderness, swelling and the like. For example, an observable difference in swelling or tenderness in even one arthritic joint is significant. Absence of swelling or tenderness in a previously affected joint is most significant. Significant objective remediation of symptoms is characterized by healing of bone cysts confirmed radiographically and decreased erythrocyte sedimentation rate (ESR) relative to normal levels (i.e., an ESR less than about 20 mm/hr is considered normal in accordance with the present invention).

"Treating" as used herein includes any measure to ameliorate, suppress, mitigate or eliminate the clinical symptoms after the onset (i.e., clinical manifestation) of juvenile rheumatoid arthritis.

"Oral" administration as used herein includes oral, enteral or intragastric administration.

"In conjunction with" as used herein means before, substantially simultaneously with or after oral administration of antacid. Of course, the immunoglobulin composition can not precede or follow administration of an antacid by so long an interval of time that the relevant effects of the substance administered first have expired. Therefore, the immunoglobulin composition should usually be administered within a therapeutically effective time. By "therapeutically effective time," as used herein, is meant a time frame in which the antacid or immunoglobulin is still active within the patient.

In a preferred embodiment, the pooled human immunoglobulin is produced by cold alcohol (e.g., ethanol) fractionation from the plasma of thousands of human volunteers according to the method of Cohn et al. (1946) J. Am. Chem. Soc., 68:459-475, incorporated herein by reference.

In another preferred embodiment, pooled human immunoglobulin is purchased from Novartis Pharmaceuticals, where it is sold under the name Immune

Globulin Intravenous (Human) Sandoglobulin®.

Sandoglobulin® is a sterile, highly purified polyvalent antibody product containing, in concentrated form, all the IgG antibodies which regularly occur in the donor population. This immunoglobulin preparation is produced by cold alcohol fractionation from the plasma of over 16,000 volunteer donors. Sandoglobulin® (IGIV) is made suitable for intravenous use by treatment at acid pH in the presence of trace amounts of pepsin. The preparation contains at least 96% of IgG and with a neutral unbuffered diluent has a pH of 6.6 ± 0.2. Most of the immunoglobulins are monomeric (7 S) IgG; the remainder consists of dimeric IgG and a small amount of polymeric IgG, traces of IgA and IgM and immunoglobulin fragments Römer J, Späth PJ: Molecular composition of immunoglobulin preparations and its relation to complement activation, in Nydegger UE (ed): Immunohemotherapy: A Guide to Immunoglobulin Prophylaxis and Therapy. London, Academic Press, 1981, p. 123. The distribution of the IgG subclasses corresponds to that of normal serum. Final container lyophilized units are prepared so as to contain 1, 3 or 6 g protein with 1.67 g sucrose and less than 20 mg NaCl per gram of protein. The lyophilized preparation is devoid of any preservative and may be reconstituted with sterile water.

In still another preferred embodiment, pooled human immunoglobulin is purchased from the Baxter Healthcare Corporation, where it is sold under the name Immune Globulin Intravenous (Human) Gammagard®. Gammagard® is a sterile, freeze dried preparation of highly purified immunoglobulin G (IgG) derived from large pools of human plasma. Gammagard® is manufactured by cold ethanol fractionation. Gammagard® contains at least about 90% IgG and trace amounts of IgA and IgM. Gammagard®, reconstituted to 5%, contains a physiological concentration of sodium chloride (approx. 8.5 mg/mL) and has a pH of 6.8 ± 0.4. The distribution of IgG subclasses is similar to that in normal plasma. Gammagard® is supplied lyophilized in 2.5, 5 or 10 g single use bottles. Each bottle of Gammagard® is furnished with a suitable volume of sterile water for reconstitution.

In yet another preferred embodiment, pooled human immunoglobulin is purchased from the Bayer Corporation, where it is sold under the name Gamimune®. Gamimune® is a sterile solution of highly purified human protein. Gamimune® contains 9-11% protein in 0.16-0.24 M glycine. At least about 90% of the protein is IgG monomer Gamimune® also contains traces of IgA and IgM. The distribution of IgG subclasses is similar to that found in normal human serum. Gamimune® like Gammagard®

and Sandoglobulin® is made by cold ethanol fractionation of pools of human plasma obtained from thousands of volunteers.

In still another preferred embodiment, pooled human immunoglobulin is purchase from Centeon, L.L.C., where it is sold under the name Immune Globulin Intravenous (Human) Gammar®. Gammar® is a sterile solution of immunoglobulin, primarily immunoglobulin G (IgG), containing 16.5 ± 15% protein. Gammar® is prepared by cold alcohol fractionation of plasma pooled from at least 1000 donors. The pH of Gammar® is 6.8 ± 0.4. Gammar® also contains approximately 0.45% sodium chloride, thimerosal, at a concentration of 0.01% and 0.3M glycine. The above-described pooled human immunoglobulin preparations are merely exemplary of the class of pooled human primarily immunoglobulin G preparations useful in accordance with the present invention.

In order to enhance the effectiveness of the introduced immunoglobulin in the treated patient and provide a clinically observable improvement, an antacid is administered in conjunction with the pooled immunoglobulin. In a preferred embodiment the immunoglobulin composition and the antacid are administered simultaneously in a unitary pharmaceutical composition. In another preferred embodiment the

immunoglobulin composition is administered at a therapeutically effective time after administration of the antacid. Preferably, the antacid is aluminum hydroxide or magnesium hydroxide such as Maalox®, Mylanta® or Tagamet® which are available commercially. Most preferably the antacid is an H2 blocker, such as Cimetidine or Ranitidine.

The dosage of antacid administered in conjunction with immunoglobulin depends on the particular H_2-blocker used. When the antacid is Mylanta®, between 15 ml and 30 ml is preferred. Most preferably the dosage of Mylanta® is 15 ml. When the cimetidine H2 blocker is used, the preferred dosage is between 400 and 800 mg per day.

The dosage of pooled human immunoglobulin administered to the patient may be varied dependent upon severity of the patient's arthritic condition and other clinical factors. Preferably, the dosage will be as small as possible while still providing a clinically observable result. The most preferable doses are those that have the largest effect in terms of alleviating the patient's arthritic condition. Dosages of the immunoglobulin composition may range from as little as 100 mg per day up to as much as 10 g per day. Dosages of 300 mg of pooled human immunoglobulin per day have been found to result in significant improvement in the

condition of patients with rheumatoid arthritis and cause little or no adverse side effects. Accordingly, 300 mg per day is a preferred dose. The present invention also contemplates dosages ranging from 3 mg/kg to about 100 mg/kg.

Although the chosen dose may be given in increments, it also may be given as a single dose. Further, although the dose of immunoglobulin may be administered at any time during the day, it is preferred that it be administered at bedtime. The patient's arthritic condition can be determined, for example, by the patient's self-assessment of his or her pain, stiffness, etc. Another way to determine the patient's arthritic condition is for a physician to examine a patient's joint tenderness, swelling and cystic growth.

It is especially advantageous to formulate the pooled human immunoglobulin in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the rheumatoid arthritic subjects to be treated, each unit containing a predetermined quantity of pooled human immunoglobulin with or without an antacid calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specifics for the novel dosage unit forms of the invention are dictated by

and directly dependent on (a) the unique characteristics of the pooled human immunoglobulin, antacid and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such a pooled human immunoglobulin for the treatment of juvenile rheumatoid arthritis herein disclosed in detail.

The pooled human immunoglobulin with or without an antacid is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore described. A unit dosage form can, for example, contain the pooled human immunoglobulin in amounts ranging from about 100 mg to about 10 g and, if desired, an antacid in an amount ranging from about 400 to 800 mg.

Clinically observable results from the administration of immunoglobulin in conjunction with antacid may be observed in as little as 2 weeks. However, it may take up to 6 weeks to obtain measurable benefit. Initial dose levels used during the first few weeks of treatment may be reduced once clinical improvement has been observed. Reductions in dose levels of up to 90% may be made after the first few weeks.

The oral treatment method in accordance with the present invention may be used to treat juvenile rheumatoid arthritis, including systemic onset,

oligoarticular and polyarticular types and other closely related autoimmune diseases such as lupus, dermatomyositis, vasculitis, scleroderma and the spondyloarthropathies. The treatment of e.g., spondyloarthropathies according to the present invention would employ the same dosages as for junveile rheumatoid arthritis and the same treatment protocol.

Demonstrations of the treatment of patients in accordance with the present invention are set forth in the following non-limiting examples.

EXAMPLE 1

An open-label study was conducted to evaluate the safety and efficacy of oral gammaglobulin. Two patients, a six year old and a 10½ year old, exhibiting severe, unremitting juvenile rheumatoid arthritis and unresponsive to conventional therapy were selected and for investigation. The patients discontinued their prescribed medical regimen, which was replaced by the administration of 300 mg of lyophilized gammaglobulin (dissolved in sterile water) daily in a single dose for six weeks. There was no evidence of toxicity as a result of receiving oral gammaglobulin. Surprisingly, both patients showed marked improvement as described fully below.

PATIENT 1

A 10½ year old boy developed systemic onset JRA at age 6 characterized by high spiking fever, intermittent rashes, polyarticular arthritis, fatique, weight loss, and ESR of 117 mm/hr. For 4 years the patient received various medications and combinations of medications. These included pulse medrol 250 mg/day, oral prednisone 20 mg/day over prolonged periods of time, methotrexate 22.5 mg/week, cyclosporin 50 mg/day, ibuprofen 1200 mg/day, indomethacin 25 mg/day and enbrel 15 mg twice weekly. Adequate control of disease activity was not achieved. In spite of optimum therapy, the

patient experienced recurrent fevers and unrelenting polyarthritis. At age 10, the patient discontinued methotrexate due to a lack of efficacy. The patient also was administered Enbrel®, but was unresponsive to enbrel as well. At this time the patient was administered 300 mg gammaglobulin orally once daily at bedtime. Within 3 to 4 weeks, the patient experienced a feeling of well being; the patient's fevers and arthritis subsided. The boy was seen by his physical therapist after 6 weeks of oral gammaglobulin. Notably, the patient was able to walk without crutches or a walker and after 3 months of therapy the patient was able to run and jump; he had been unable to walk without assistance since the onset of his disease. At this time the patient's ESR was 20 mm/hr compared to an ESR of greater than 100 mm/hr before taking oral gammaglobulin. After 6 months of therapy, the patient remains in remission. X-rays were taken after 6 months of oral gammaglobulin and showed complete healing of multiple large bone cysts. The patient continues to take 300 mg oral gammaglobulin daily without any side effects.

PATIENT 2

A 6-year old girl developed polyarticular onset JRA at age 1½. For the past 4 years she was treated with multiple drug therapy, and her current therapy included prednisone, methotrexate, cyclosporin, and Enbrel®. In

spite of this aggressive therapy, the patient was resistant to therapy, exhibiting a poor clinical response. The patient had to be carried upstairs to her bedroom and she could not descend the stairs without help. The patient's pain was so severe that she was unable to sleep due to severe pain from turning in bed.

At age six she was started on 300 mg of oral gammaglobulin at bedtime. Within one week of therapy the patient informed her mother that she was beginning to feel well. After 2 weeks of therapy she began to sleep through the night for the first time in 4 years. The patient reported that the oral gammaglobulin was responsible for her improvement and requested the medication at night. After 3 weeks of therapy dramatic improvement in the swelling of the patient's ankles were observed by the patient's mother, and the girl was able to climb and descend stairs without help for the first time in 4 years.

The child was able to ambulate better with less pain, and her play was more vigorous. The patient's physician evaluated her and documented at least 50% clinical improvement in only 3 weeks. Because the patient was scheduled to enter another clinical trial, the oral gammaglobulin was discontinued. She was examined again two weeks after discontinuing the oral gammaglobulin, and the same physician documented a 20%

flare of her arthritis. The patient did not experience any side effects from the oral gammaglobulin.

WHAT IS CLAIMED IS:

1. A method of treating juvenile rheumatoid arthritis in a patient comprising orally administering to said patient an immunoglobulin composition comprising pooled human immunoglobulin in an amount sufficient to provide a clinically observable improvement in the rheumatoid arthritis of said patient.

2. The method of Claim 1, further comprising an antacid.

3. The method of Claim 1 wherein said immunoglobulin composition comprises pooled human polyclonal IgG antibodies.

4. The method of Claim 1 wherein said immunoglobulin composition is selected from the group consisting of Sandoglobulin®, Gammagard® or Gamimune®.

5. The method of Claim 2 wherein said antacid is selected from the group consisting of aluminum hydroxide, magnesium hydroxide, cimetidine or ranitidine.

6. The method of Claim 1 wherein the amount of immunoglobulin composition which is administered to said patient is between 100 mg to 10 g per day.

7. The method of Claim 5 wherein the amount of immunoglobulin composition which is administered to said patient is about 300 mg per day.

8. The method of Claim 2 wherein the amount of antacid which is administered to said patient is between 200 mg to 800 mg per day.

9. The method of Claim 8 wherein the amount of antacid which is administered to said patient is about 400 mg per day.

10. The method of Claim 1 wherein said immunoglobulin composition is administered in a unit dosage form.

11. The method of Claim 2 wherein said antacid is administered in a unit dosage form.

12. The method of Claim 1 wherein said immunoglobulin composition is in a powdered form.

13. The method of Claim 1 wherein said immunoglobulin composition is dispersed in pharmaceutically acceptable carrier.

14. The method of Claim 2 wherein said immunoglobulin composition and said antacid are administered simultaneously to said patient.

15. The method of Claim 2 wherein said immunoglobulin composition is administered at a therapeutically effective time after administration of said antacid.

16. A pharmaceutical composition comprising pooled human immunoglobulin, an antacid and a pharmaceutically acceptable carrier.

17. The pharmaceutical composition of Claim 1 wherein said pooled human immunoglobulin is Sandoglobulin®.

18. The pharmaceutical composition of Claim 16 wherein said antacid is cimetidine.